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### **Efficacy and safety of pegylated liposomal doxorubicin in primary cutaneous B-cell lymphomas and comparison with the commonly**

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## ORIGINAL ARTICLE

# Efficacy and safety of pegylated liposomal doxorubicin in primary cutaneous B-cell lymphomas and comparison with the commonly used therapies

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## Abstract

**Objectives:** The therapy of advanced, relapsed or refractory primary cutaneous lymphomas is often unsatisfactory. Recent data indicate a favourable pharmacokinetic, pharmacodynamic and toxicity profile of pegylated liposomal doxorubicin (Peg-Doxo) in primary cutaneous T-cell lymphomas, while in primary cutaneous B-cell lymphomas (PCBCLs), the drug efficacy has never been assessed so far. **Methods:** We performed a prospective phase II pilot clinical trial of Peg-Doxo monotherapy (20 mg/m<sup>2</sup>) in PCBCLs. One patient had a marginal zone B-cell lymphoma and four were affected by diffuse large B-cell lymphoma-leg type, all with widespread nodular lesions. **Results:** All the patients achieved a complete response (CR = 100%) in a short period of time (median 3 months), even when pretreated with radio-chemotherapy. Two experienced a relapse. At follow-up, one patient died for progressive disease; four are in CR after 5, 52, 63 and 69 months. As concerning the toxicity profile, the treatment was well-tolerated, no one decreased or delayed the dose. The haematological toxicity was mild with only one case of grade III neutropenia; a patient showed a grade I neurotoxicity. Dermatological toxicity, in particular the palmar-plantar erythrodysesthesia, did not occurred, probably because of both the low dosages of Peg-Doxo monotherapy and the oral prophylaxis with pyridoxine. **Conclusions:** In spite of the small number of patients, it emerges that monochemotherapy with Peg-Doxo has a significantly high clinical activity and a good safety profile in PCBCLs, even in aggressive forms, compared with other therapeutic regimens, which are completely reviewed. It suggests the need of further investigations in this field.

**Key words** primary cutaneous B-cell lymphomas; pegylated liposomal doxorubicin; primary cutaneous lymphomas; monochemotherapy

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Doxorubicin is frequently used in the treatment of lymphomas; the pegylated liposomal formulation of the drug (Peg-Doxo) has significantly improved its therapeutic index, reducing the toxic adverse effects. Peg-Doxo shows a similar efficacy, being less cardiotoxic, producing less nausea and vomiting and only mild myelosuppression and alopecia (1). The drug, carried in stealth liposomes able to

escape the interception by the immune system, shows a prolonged circulation time and a propensity for extravasating through the leaky vessels of the tumour tissues; it results the increased concentration of the drug in target tissues and the decreased toxicity to normal cells (2). Originally approved for the treatment of metastatic breast cancer, in advanced ovarian cancer and in Kaposi's sarcoma, Peg-Doxo has

been successfully used in other solid tumours and in haematological neoplasms: refractory-relapsed multiple myeloma (3), indolent non-Hodgkin's lymphoma (NHL) in monotherapy (4), as well as in aggressive lymphoma (5), even in elderly patients (6, 7), in cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) plus rituximab regimen (8, 9), relapsing Hodgkin's lymphoma (10). It has been successfully used also in primary cutaneous lymphomas (PCLs), which constitute the second most common group of extranodal NHLs after the gastrointestinal ones, with an incidence of about 1 per 100 000 inhabitants per year (11). Peg-Doxo has been successfully used particularly in primary cutaneous T-cell lymphomas (PCTCLs). The largest study in this setting was conducted in recalcitrant/recurrent PCTCLs. Thirty-four patients received Peg-Doxo monotherapy (20 mg/m<sup>2</sup>) and obtained 44% complete response (CR), 88% overall response (OR) with a disease free survival (DFS) of 13 months, event free survival (EFS) of 12 months and overall survival (OS) of 18 months (12). In another experience, 10 patients with IV B stage Mycosis Fungoides (MF) obtained three partial responses (PR) and two stable diseases (SD) with a median OS of five months (13), while in 2006, were described six relapsing, refractory MF patients in stage IB-IVA who were treated with Peg-Doxo monotherapy (20 mg/m<sup>2</sup>): one patient obtained a CR, four a PR and one a SD (14). Our experience in 19 advanced and relapsed PCTCLs treated with Peg-Doxo monotherapy (20 mg/m<sup>2</sup>) showed an OR and CR rates of 84% and 42% respectively and a mild toxicity (11% grade III/IV); after a maximum 46 month-follow-up, median OS, EFS and PFS survival were 34, 18 and 19 months and the OS, EFS and PFS rates at 46 months were 44%, 30% and 37% respectively (15). The dose escalation to 40 mg/m<sup>2</sup> increases toxic effects, but does not seem to improve the effectiveness as recently reported in 25 patients (16). Peg-Doxo has not been evaluated in primary cutaneous B-cell lymphomas (PCBCLs) to date, which account for about 25% of all PCLs. According to the recent WHO-EORTC consensus classification, PCBCLs include (11): primary cutaneous marginal-zone B-cell lymphomas (PCMZLs), follicle-centre lymphomas (PCFCLs), diffuse large B-cell lymphomas, leg type (PCLBCLs-LT). More rare types are diffuse large B-cell lymphoma-other, lymphoblastic lymphoma and intravascular large B-cell lymphoma. The therapy of advanced, relapsed or refractory primary cutaneous B-cell lymphomas is often unsatisfactory. Systemic polychemotherapy with CHOP or CHOP-like regimens represent a standard therapy in PCLBCL (17, 18), and sometimes even in particularly refractory or relapsing PCMZL and PCFCL especially in patients presenting with diffuse and numerous cutaneous lesions (19). Starting from the encouraging results in B-cell systemic lymphomas and in PCTCLs, we performed a prospective phase II pilot clinical trial of Peg-Doxo

monotherapy (20 mg/m<sup>2</sup>) in PCBCL. We report preliminary results in five patients, which are herein analyzed together with a review of literature on the treatment of PCBCL.

## Patients and methods

### Patients

Five patients, affected by PCBCL, underwent a complete evaluation including laboratory analyses, clinical history, physical examination and identification of all skin lesions as patches, plaques or nodules. The histological diagnoses have been made or reviewed according to the recent consensus classification (11); besides, the new TNM staging system (according to Tumour, Node, Metastasis) was used (20). Total body CT scan, bone marrow trephine biopsy and echocardiogram were performed before starting treatment. Ethical approval of the study was granted and all the patients gave their written informed consent.

### Treatment, response and toxicity assessment

All patients received intravenous pegylated liposomal doxorubicin, Peg-Doxo (Caelyx®, Schering-Plough, Bruxelles, Belgio) at the dosage of 20 mg/m<sup>2</sup> every 3–4 wk, preceded by an antiemetic prophylaxis. Supportive therapy consisted of oral pyridoxine 300 mg daily from the beginning of the treatment until 1 month after its discontinuation, to prevent the palmar-plantar erythrodysesthesia (PPE) or hand-foot (HF) syndrome (21–23). Responses, which were lasting 4 wk at least, were defined according to Cheson's criteria (24) and assessed by two independent observers who were blind to each other's evaluation. Complete remission (CR) was defined as the complete clearance of all skin lesions, i.e. absence of clinically detectable residual disease; relapse was defined as any clinically detectable disease after a CR (24). Toxicity was graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 3 criteria (25); skin toxicity was particularly evaluated, as described by Lotem *et al.* (22).

### Results

All patients had multiple skin lesions, without lymph node involvement and with no evidence of extracutaneous non-lymph nodal disease. Three patients had a widespread skin involvement, with numerous lesions involving ≥3 non-contiguous body regions, T3b according to TNM system (20). Two patients had a regional skin involvement with multiple lesions limited to one or two contiguous body regions and with all-disease-encompassing in a >15-cm and <30-cm-diameter (T2b) or in

**Table 1** Clinico-pathological characteristics of the patients before starting Peg-Doxo treatment, response and follow-up

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Gender	F	M	M	M	M
Age (yrs)	38	55	53	75	55
Disease history (months)	23	35	10	2	2
WHO/EORTC histological type	PCMZL	PCLBCL-LT	PCLBCL-LT	PCLBCL-LT	PCLBCL-LT
Pretreatment	R; Gem	R; R-CVP	R	None	None
Type of lesions	Nodules and plaques	Nodules and plaques	Nodules and plaques	Nodules and plaques	Nodules
Body regions	HN, RLAH, LLAH, RUL, RLLF, LUL	C, AG	UB	C, UB, RLLF, LLLF	RUA, RLAH, LUA, LLAH
TNM	T3b, N0, M0	T2c, N0, M0	T2b, N0, M0	T3b, N0, M0	T3b, N0, M0
PS	0	0	1	1	0
No. infusions	4	8	8	6	6
LDH	Normal	Normal	High	High	High
$\beta_2$ microglobulin	Normal	Normal	Normal	High	Normal
Itching	No	Yes	No	No	Yes
Max response (months)	2	2	3	4	3
Response	Complete	Complete	Complete	Complete	Complete
Toxicity (grade and type)	No	No	No	III neutropenia	I neurotoxicity
Relapse (months)	Yes (8)	No	No	Yes (11)	No
Post-treatment	IFN; Rit	–	–	CBVD; Rit	–
Status at last follow-up	AW; CR	AW; CR	AW; CR	DOD	AW; CR
Follow-up (months)	52	69	5	25	63

Pretreatment: R, radiotherapy; Gem, gemcitabine; R-CVP, rituximab, cyclophosphamide, vincristine, prednisone.

Body regions according to TNM system (23): HN, head and neck; C, chest; AG, abdominal and genital; UB, upper back; LUA, right upper arm; RLAH, right lower arm and hand; LUA, left upper arm; LLAH, left lower arm and hand; RUL, right upper leg; RLLF, right lower leg and feet; LUL, left upper leg; LLLF, left lower leg and feet.

TNM (23): T2, regional skin involvement: multiple lesions limited to 1 body region or 2 contiguous body regions; T2a, all-disease-encompassing in a <15-cm-diameter circular area; T2b, all-disease-encompassing in a >15-cm and <30-cm-diameter circular area; T2c, all-disease-encompassing in a >30-cm-diameter circular area; T3, generalized skin involvement; T3a, multiple lesions involving 2 non-contiguous body regions; T3b, multiple lesions involving  $\geq 3$  body regions. N0, no clinical or pathological lymph node involvement; M0, no evidence of extracutaneous non-lymph node disease.

PS: performance status according to WHO.

Relapse: time from Peg-Doxo to relapse.

Post-treatment: IFN, interferon; Rit, rituximab; CBVD, Peg-Doxo, bleomycin, vinblastine, dacarbazine.

Status: AW, alive and well; DOD, dead of disease.

Follow-up: months from Peg-Doxo to last follow up or death.

a >30-cm-diameter (T2c) circular area. One was affected by indolent and four by aggressive PCBCL. In two patients, the treatment was first-line (Table 1).

### Patient 1

A 38-yr-old woman was diagnosed with PCMZL 23 months before; she had been treated with radiotherapy, followed by gemcitabine for a massive recurrence, thus achieving a CR. She came with multiple generalized nodular lesions and grouped plaques on the head, neck, both lower arms and upper legs and right lower leg (T3b, N0, M0). The performance status (PS) according to WHO was 0 and she had no systemic symptoms. The skin biopsy showed a diffuse dermal infiltrate, not involving the epidermis, structured in follicles with reactive germinal centers; they were surrounded by small

sized monomorphic lymphocytes with irregular nuclei and pale cytoplasm, showing a B cell CD20 + immunophenotype, without expression of CD10, BCL6, BCL1, MUM1 and with low proliferative index (Mib-1 positivity in 5%), surrounded by a rich plasmacellular population, expressing CD138 and CD79a and with monotypic expression of cytoplasmic immunoglobulin k light chain: the whole picture was interpreted as a relapse of PCMZL. The association with *Borrelia Burgdorferi* infection was ruled out, both with serological tests and the molecular detection by PCR-technique analysis in the formalin-fixed and paraffin-embedded tissues samples, as previously reported (26). The total body CT scan and bone marrow trephine biopsy were negative and neither the t(11;14) and t(14;18) nor BCL1 protein expression were demonstrated. She was treated with Peg-Doxo

monotherapy and after four infusions reached a clinical CR. She relapsed after 8 months and was treated with interferon, reaching a PR, i.e. reduction  $\geq 50\%$  of pre-existing skin lesions and also  $\geq 50\%$  resolution of nodules and plaques in macular lesions, with no evidence of new lesions. The CR was obtained through a consolidation with systemic rituximab. A second relapse was successfully treated with rituximab, achieving a CR, now still lasting 52 months after Peg-Doxo therapy.

#### Patient 2

A 55-yr-old man, PS 0, affected by PCLBCL-LT, firstly diagnosed 35 months before, had been successfully previously treated with radiotherapy and R-CVP chemotherapy (rituximab and cyclophosphamide, vincristine, prednisone). He presented multifocal itching plaques and tumours on the chest and abdomen (T2c, N0, M0). The cutaneous biopsy specimen showed a diffuse monotonous population of blasts with round nuclei, extending into the subcutaneous tissue; the blasts were immunoreactive for CD20, expressed BCL2, MUM1, showed a high proliferative index (Mib-1 positivity in 75% of cells) and were negative for BCL6. All the staging procedures were negative, the diagnosis of PCLBCL-LT was confirmed and Peg-Doxo treatment started, with eight infusions. The patient reached a CR after 2 months, still lasting 69 months later.

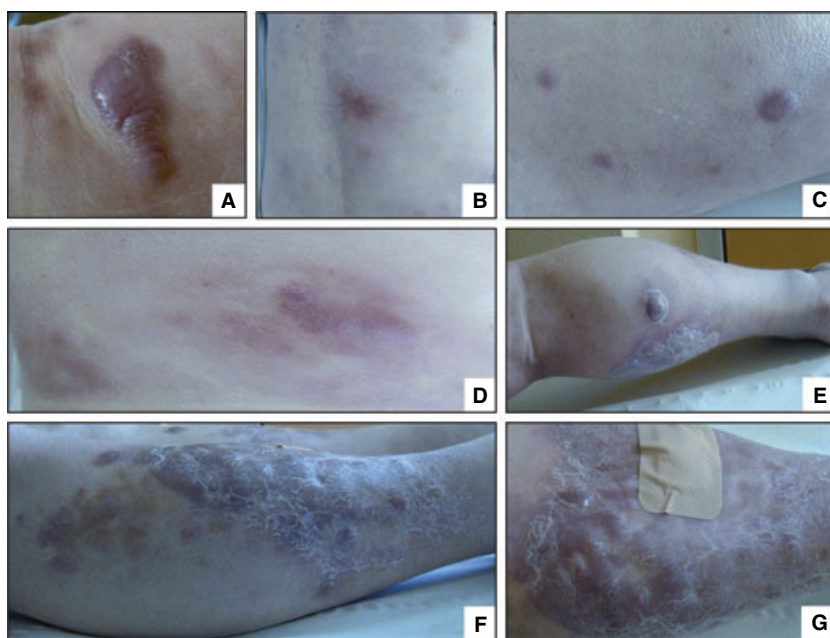
#### Patient 3

A 53-yr-old man, PS 1, was affected by PCLBCL-LT, previously treated with radiotherapy. He presented growing nodules and plaques on upper back, i.e. T2b, N0,

M0. The histological examination revealed a diffuse infiltrate of large round cells, positive for CD20, MUM1, with a variable expression of BCL6 and focal expression of BCL2, which was interpreted as a phenotypic variant of LBCL-LT. He was treated with eight courses of Peg-Doxo and reached a CR.

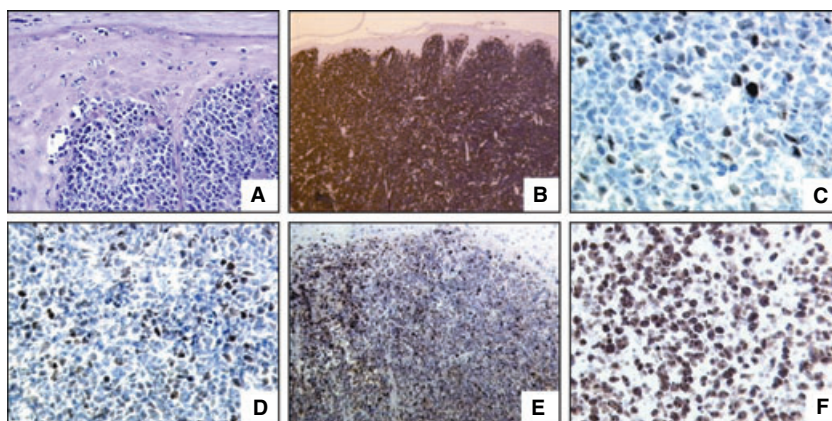
#### Patient 4

A 75-yr-old man, PS 1, presented multifocal rapidly growing plaques and tumours of 3–4 cm on the chest, upper back, both lower legs and feet, without systemic symptoms (Fig. 1). He belonged to T3b, N0, M0 group. The biopsy specimen showed a diffuse monotonous population of blasts with immunoblastic appearance involving the skin and infiltrating the epidermis; they were diffusely positive for CD20, negative for CD10, positive for BCL6, BCL2, MUM1, and highly proliferating with an elevated Mib-1 immunostaining (Fig. 2). The diagnosis was PCLBCL-LT. He started Peg-Doxo therapy and obtained a very good partial remission (VGPR) after only two cycles, i.e. a reduction  $> 75\%$  of skin lesions and also  $> 75\%$  resolution of nodules and plaques in macular lesions, with no evidence of any new lesions (Fig. 3). A clinical and histological CR was reached after six cycles, so the patient received a maintenance therapy with interferon. The first cutaneous recurrence occurred after 11 months and was treated with four courses of CBVD scheme (peg-doxo 12 mg/m<sup>2</sup>, bleomycin, vinblastine, dacarbazine), followed by rituximab, again resulting in a clinical and histological CR. After 4 months, a second relapse was recorded, showing the same histopathological

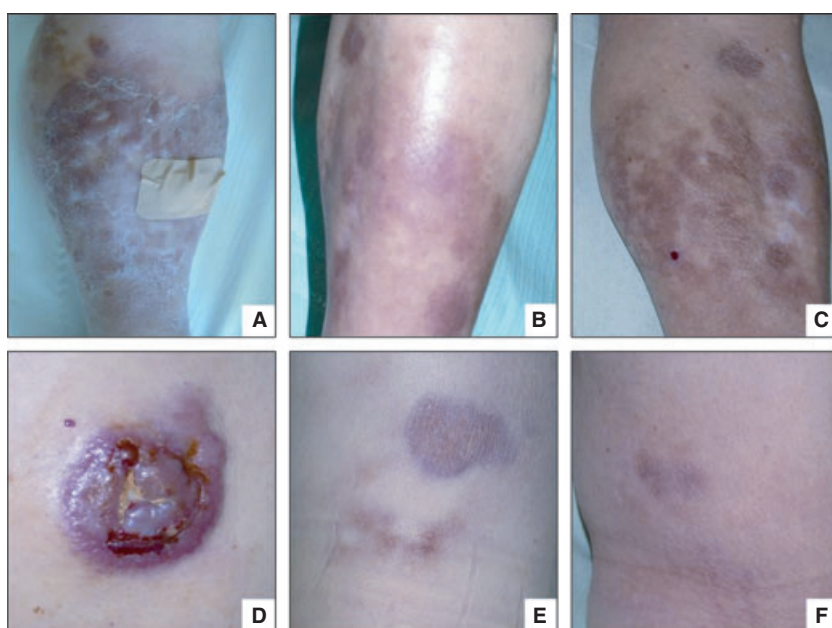


**Figure 1** Patient number 4: PCLBCL-LT. A 75-yr-old man presented multifocal rapidly growing infiltrating plaques and tumours of 3–4 cm on the trunk (A, B, D) and both lower legs (C, E, F, G).





**Figure 2** Patient number 4: PCLBCL-LT. Diffuse large B-cell lymphoma involving the skin and infiltrating the epidermis; cells are large blasts with immunoblastic appearance (H and E) (A). Blasts are diffusely positive for CD20 (B), negative for CD10 (C), positive for BCL6 (D), BCL2 (E), and highly proliferating with Mib-1 immunostaining (F).



**Figure 3** Patient number 4: PCLBCL-LT. At diagnosis (A, D), after two cycles of Peg-Doxo monotherapy (B, E), after four cycles of Peg-Doxo (C, F). A, B, C: lower legs; D, E, F: trunk.

pattern as at diagnosis. Besides the cutaneous lesions, the patient presented a progressive headache. A brain CT scan and then MRI revealed in the left side of the corpus callosum a nodular lesion of 2.5 cm, with a homogeneous enhancement after i.v. administration of contrast medium; besides, other hyperintense in T2-weighted lesions, with inhomogeneous enhancement after contrast medium, were localized in left frontal lobe, the paraventricular left region along the internal capsule and the subependymal tissue of right fourth ventricle; the cerebrospinal fluid and the bone marrow were normal. The  $^{18}\text{F}$ FDG-CT/PET showed foci of high hyperactivity in correspondence of the corpus callosum and in paramedian posterior right region of the fourth ventricle, a cerebral PCBCL localization was considered most likely. Brain radiotherapy was started, but a few days later, the patient developed pneumonia and died because of pulmonary embolism, 27 months after the first diagnosis.

### Patient 5

A 55-yr-old man, PS 0, came to our attention with a 1-month-history of rapidly growing multiple diffuse itching nodules of both upper and lower arms, whose histopathological examination revealed the aggressive pattern, confirmed by immunohistochemical detection of CD20, BCL6, BCL2, MUM1 and elevated Mib-1. The man was affected by PCLBCL-LT, stage T3b, M0, N0, according to TNM classification. He was treated with six courses of Peg-Doxo monotherapy, which was well tolerated, and a CR was reached still lasting after 63 months.

### Toxicity

Peg-Doxo monotherapy was well-tolerated and in no patient, the dose was decreased or the infusion was delayed (Table 1). One patient had a reversible mild

grade I neurotoxicity; the haematological toxicity was mild with one case of grade III neutropenia successfully treated with granulocyte colony-stimulating factor (G-CSF). Nobody experienced a dermatological toxicity (22), like follicular rash, intertrigolike eruption or the formation of melanotic macules; in particular, the palmar–plantar erythrodysesthesia, frequently reported in patients treated with Peg-Doxo, was not recorded (21–23).

## Discussion

The present study constitutes the first report on pegylated liposomal doxorubicin in patients affected by primary cutaneous B-cell lymphomas. A monochemotherapy with Peg-Doxo at the dosage of 20 mg/m<sup>2</sup> has been used. All the five patients achieved a complete response (CR = 100%), in a short period (median 3 months), even when they had been pretreated with radio-chemotherapy or when experiencing the most aggressive forms, like PCLBCL-LT. The treatment was well-tolerated and safe, confirming that Peg-Doxo ameliorates the common side effects of conventional doxorubicin (2). Severe mucocutaneous reactions, however, can occur with repeated doses of Peg-Doxo, mostly the palmar–plantar erythrodysesthesia (PPE) or hand-foot (HF) syndrome, as Peg-Doxo has a particular skin-tropism suggested by pharmacokinetic studies (1, 21). The PPE is characterized by tingling, dysesthesia, erythema and swelling, followed in severe cases by skin desquamation, crusting, ulceration and necrosis of the epidermis; it affects hands, feet and other skin areas under prolonged friction or pressure (21, 22). Different pathophysiological mechanisms are suggested: Peg-Doxo, excreted from sweat glands, penetrates into the corneum stratum producing local oxidative and inflammatory reactions; it has a direct cytotoxic effect or it is extravasated from the deep microvessels through the local pressure. PPE incidence is dose- and schedule-dependent and influenced by peak drug concentration, total cumulative dose and infusion time (21–23). It is reversible with complete healing and is unrelated to chemotherapy vesicant effect. PPE is frequently reported in patients with cancer treated with Peg-Doxo: about 50% of all patients with solid neoplasms, who received the currently approved dose of 50 mg/m<sup>2</sup> every 4 wk, experienced PPE and about 20% of them a grade III PPE. When PPE develops, Peg-Doxo dose reduction, schedule modification, ultimately drug withdrawal are considered; some authors have suggested prophylaxis or treatment with pyridoxine, dexamethasone, amifostine and celecoxib (21). In our patients, the PPE did not occurred; probably, it was prevented by the prophylaxis with pyridoxine, as well as by the utilization of lower dosages in monochemotherapy of Peg-Doxo,

compared with the higher doses and to the polychemotherapeutic regimes commonly used in other solid neoplasms.

For a comparison of our results with the common treatment modalities applied in PCBCL, it is not surprising to find in the literature the absence of controlled and randomized trials in PCBCL. Very recently, EORTC, Cutaneous Lymphoma Group and the International Society for Cutaneous Lymphomas published consensus recommendations for the management of the main groups of PCBCL; they are mainly based on retrospective studies and small cohort studies (27). Besides chemotherapy, the most widely accepted treatments of PCBCLs are the complete excision of localized lesions (27), radiotherapy (28), topical or intralesional steroids (29), systemic and intralesional interferon- $\alpha$  and interferon- $\gamma$  (30), rituximab (31, 32). More experimental therapies include denileukin diftitox (33), new biological agents (29, 34) and Yttrium-90-ibritumomab tiuxetan or 131I-tositumomab radioimmunotherapy (29, 35).

In indolent primary cutaneous B-cell lymphomas, i.e. PCMZL and PCFCL, one or few localized small lesions can be cured surgically through a complete excision; in some studies, about 95% of the patients obtained a CR, although 50% of them developed new skin lesions; a better definition of tumour-resection free margins is probably necessary (27). Topical or intralesional steroids can be used to treat patients with individual symptomatic skin lesions (29). Systemic and intralesional interferon- $\alpha$  and interferon- $\gamma$  have been reported, with dosages from 1 to 6 million IU three times a week, according to the extent of the lesions (30). Similar to the gastric MALT lymphoma treatment where the aim of therapy is to eradicate *Helicobacter pylori* infection, in PCMZL patients, the eradication of *Borrelia burgdorferi* infection – if any – by specific antibiotic therapy, especially systemic cephalosporins, often allows a complete remission (26, 36). Many authors suggest that this therapy should be always used before more aggressive treatments, but the efficacy of antibiotics is not well-documented (37). Like in nodal indolent NHL, in PCMZL and PCFCL patients, a wait and see policy can be sometimes considered for the initial management, with subsequent radiotherapy towards one or few symptomatic skin lesions (27). In the great majority of these patients, the chemotherapy is not considered as first line treatment (28). Since past years, there was a general consensus that PCBCLs presenting with solitary or localized skin lesions should be treated with optimal dose of radiotherapy, irrespective of histological type, as they have a good prognosis and very rarely develop extracutaneous relapses. The optimal therapy for patients showing multifocal skin nodules or plaques appeared more problematic with some reports describing an unfavourable prognosis

in the multifocal PCBCLs; consequently, many suggested an aggressive multiagent chemotherapy. Recent studies revealed that in PCFCL and PCMZL, even when presenting with lesions at different sites, the irradiation of all visible skin lesions, with multiple radiation fields, may be preferable to chemotherapy, because of less toxicity and similar effectiveness, as these patients share the same low tendency to develop extracutaneous disease and the same good prognosis of individuals with localized skin lesions (19). The reported cumulative doses per irradiation field are mostly between 20 and 45 Gy. In almost all patients with PCMZL treated with radiotherapy, an initial CR was observed, even if about 50% of patients showed a cutaneous relapse, while extracutaneous progression being very rare. Moreover, new cutaneous lesion can be frequently treated with the same therapy used as first line. The largest studies in PCFCL described a relapse in about 30% of patients (28, 38). Multifocal PCFCLs occurring in the leg have a worse prognosis than PCFCL at other sites, similar to PCBCL-LT (18). In patients with indolent PCLs, systemic chemotherapy may be effective in yet particularly recalcitrant, refractory and relapsing forms, especially presenting with widespread, numerous and extremely thick tumours occurring in non-related parts of the skin, in which radiotherapy seems to be unsuitable (19). In a recent review among 300 PCBCL patients, only 7% to 14% among indolent types underwent chemotherapy (18). Among chemotherapeutic agents, chlorambucil may be used in relapsing and/or multifocal skin lesions of PCMZL and in particular, in the elderly, in patients with diffuse skin lesions, a 50% rate of CR has been reported (37, 39). Local chemotherapy has been used in the past for PCLs: intralesional cisplatin gel in PCFCLs (40) or topical carmustine (BCNU), more commonly used in PCTCL (41). Reports about agents used in indolent nodal B-cell NHL, like fludarabine, cladribine and pentostatin are lacking in PCBCL. Few data exist about polychemotherapy in indolent PCLs; in PCMZL, in particular, it is very rare; CHOP or CHOP like regimens have been used. Rituximab has been used in both PCMZL and PCFCL as systemic treatment at the dosage of 375 mg/m<sup>2</sup> i.v. once weekly and as topical intralesional treatment at the dosage of 5–30 mg per application once or 2–3 times a week. Intralesional rituximab resulted safe and effective, similar to i.v. therapy. It can induce a complete disappearance of B-cells in the peripheral blood, suggesting a systemic effect (31); nevertheless relapse of CBCL with new lesions at distinct sites can be observed more frequently after intralesional treatment (32). The patient 1 constitutes an example of an indolent form, PCMZL, but with an extensive skin involvement, previously already treated, in which radiotherapy was considered inappropriate and a systemic treatment was

therefore necessary. Peg-Doxo showed a good clinical outcome, although it probably did not change the natural history of the disease, which is a frequently relapsing cutaneous disease. More investigations in indolent PCBCL are required.

The primary cutaneous large B-cell lymphomas (PCLBCLs) represent a separate group including the leg-type and other, with a general unfavourable prognosis, because of a different genetic pattern expression, like BCL2 and Fas-ligand (18, 42). PCLBCL-LT predominantly affects elderly patients, has a high tendency to extracutaneous dissemination and a high mortality rate; the presence of multifocal skin lesions might represent an additional risk factor. Less aggressive therapies are sometimes compulsory because of the advanced age or the presence of different comorbidities in the patients, but they never result in a sustained CR. In the recent review among 300 PCBCL patients, up to 25% of aggressive ones (PCLBCL) underwent chemotherapy (18). Before the eighties, patients with localized PCLBCL were treated only with radiotherapy, but later, the treatment was changed to doxorubicin-containing regimens, an approach giving results well-correlated with the concepts and outcomes of early Ann-Arbor stage of all sites (stage IE) (17, 43). Only very localized PCLBCL in older patients, not suitable for aggressive treatment, could be managed through an irradiative treatment. It is not clear if radiotherapy should be proposed as standard treatment in such rare cases presenting with a small solitary lesion (27). On the contrary, the most commonly described PCLBCLs presenting with multifocal lesions must be treated with systemic chemotherapy, sometimes completed with adjuvant radiotherapy. CHOP or CHOP-like regimens constitute the golden standard among the polychemotherapeutic schemes: in 46 PCBCL, the OR rate was 98% with 89% CR rate and 33% relapse rate (44). CHOP regimen appears to be preferred to COP as it reduces relapse rates (43). A case has been successfully treated with MACOP-B polychemotherapy showing a good response and a DFS of more than 3 yr (45). Even the systemic administration of rituximab appears a good chance, in particular, in the elderly; in very aggressive or in plurirelapsing lymphomas, in case with systemic involvement, the combination of rituximab with anthracycline-containing chemotherapies may be proposed, even if data about response and prolonged follow-up are still lacking (17, 31). The association of rituximab with single-dose cyclophosphamide in seven relapsing PCBCL gave encouraging results, even if a short follow-up period has been reported, in particular in terms of DFS, with OR rate of 85% and CR 71% (46).

Finally, in exceedingly rare aggressive, refractory or plurirelapsing PCBCLs, the autologous and even



allogeneic bone marrow as well as stem cell transplantation can be proposed, even if these procedures are associated with significant morbidity and mortality, especially in the elderly (47).

Among our patients, all the four with aggressive forms (PCLBCL-LT) showed a CR in a short period, which was long lasting in two of them (69 and 63 months respectively), even if one of them had a refractory, relapsing disease (Patient 2). The particular skin-tropism of Peg-Doxo (1, 21) probably accounts for the high rate of CR in such very aggressive cutaneous lymphoma. The patient 4 died for relapsing and progressive disease. He constitutes a rare example of extracutaneous recurrence in the central nervous system (CNS). The overall risk of secondary CNS involvement in NHL is about 5%. With regards to PCLs, this complication is mainly reported in patients with PCTCL, mostly in stage IV B Mycosis Fungoides and, among B histological types, in intravascular lymphoma, but very rarely in other PCBCL, which accounts for 2% of cases and is related to death, according to the published data from the Dutch Cutaneous Lymphoma Registry (48, 49).

In conclusion, as regarding this prospective phase II pilot clinical trial, monotherapy with Peg-Doxo shows a significantly high clinical activity and a good safety profile in PCBCLs, compared with other mono- and poly-chemotherapeutic regimens reported in the literature,

The major limitations of this pilot study are that the case-number is small and that one patient has a very short follow-up period (5 months); on the contrary, the other three alive patients have quite long follow-up period (52, 69 and 63 months respectively). It suggests the need of further and extended investigations in PCBCLs, even randomized studies. The association of Peg-Doxo with other drugs, especially rituximab, should be considered.

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## References

- Charrois GJ, Allen TM. Multiple injections of pegylated liposomal doxorubicin: pharmacokinetics and therapeutic activity. *J Pharmacol Exp Ther* 2003;**306**:1058–67.
- Cattel L, Ceruti M, Dosio F. From conventional to stealth liposomes: a new frontier in cancer chemotherapy. *J Chemother* 2004;**16**:94–7.
- Orlowski RZ, Nagler A, Sonneveld P, *et al.* Randomized phase III study of pegylated liposomal doxorubicin plus bortezomib compared with bortezomib alone in relapsed or refractory multiple myeloma: combination therapy improves time to progression. *J Clin Oncol* 2007;**25**:3892–901.
- Di Bella NJ, Khan MM, Dakhil SR, Logie KW, Marsland TA, Weinstein RE, Mirabel MY, Asmar L. Pegylated liposomal doxorubicin as single-agent treatment of low-grade non-Hodgkin's lymphoma: a phase II multicenter study. *Clin Lymphoma* 2003;**3**:235–40.
- Avilés A, Neri N, Castañeda C, Talavera A, Huerta-Guzmán J, González M. Pegylated liposomal doxorubicin in combination chemotherapy in the treatment of previously untreated aggressive diffuse large-B-cell lymphoma. *Med Oncol* 2002;**19**:55–8.
- Martino R, Perea G, Caballero MD, Mateos MV, Ribera JM, de Oteyza JP, Arranz R, Terol MJ, Sierra J, San Miguel JF. Cyclophosphamide, pegylated liposomal doxorubicin (Caelyx), vincristine and prednisone (CCOP) in elderly patients with diffuse large B-cell lymphoma: results from a prospective phase II study. *Haematologica* 2002;**87**:822–7.
- Tsavaris N, Kosmas C, Vadiaka M, Giannouli S, Siakantaris MP, Vassilakopoulos T, Pangalis GA. Pegylated liposomal doxorubicin in the CHOP regimen for older patients with aggressive (stages III/IV) non-Hodgkin's lymphoma. *Anticancer Res* 2002;**22**:1845–8.
- Visani G, Guiducci B, D'Adamo F, *et al.* Cyclophosphamide, pegylated liposomal doxorubicin, vincristine and prednisone (CDOP) plus rituximab is effective and well tolerated in poor performance status elderly patients with non-Hodgkin's lymphoma. *Leuk Lymphoma* 2005;**46**:477–9.
- Zaja F, Tomadini V, Zaccaria A, *et al.* CHOP-rituximab with pegylated liposomal doxorubicin for the treatment of elderly patients with diffuse large B-cell lymphoma. *Leuk Lymphoma* 2006;**47**:2174–80.
- Bartlett NL, Niedzwiecki D, Johnson JL, Friedberg JW, Johnson KB, van Besien K, Zelenetz AD, Cheson BD, Canellos GP; Cancer Leukemia Group B. Gemcitabine, vinorelbine, and pegylated liposomal doxorubicin (GVD), a salvage regimen in relapsed Hodgkin's lymphoma: CALGB 59804. *Ann Oncol* 2007;**18**:1071–9.
- Willemze R, Jaffe ES, Burg G, *et al.* WHO-EORTC classification for cutaneous lymphomas. *Blood* 2005;**105**:3768–85.
- Wollina U, Dummer R, Brockmeyer NH, Konrad H, Busch JO, Kaatz M, Knopf B, Koch HJ, Hauschild A. Multicenter study of pegylated liposomal doxorubicin in patients with cutaneous T-cell lymphoma. *Cancer* 2003;**98**:993–1001.
- Di Lorenzo G, Di Trollo R, Delfino M, De Placido S. Pegylated liposomal doxorubicin in stage IV B mycosis fungoides. *Br J Dermatol* 2005;**153**:183–5.
- Lybaek D, Iversen L. Pegylated liposomal doxorubicin in the treatment of mycosis fungoides. *Acta Derm Venereol* 2006;**86**:545–7.

15. Pulini S, Rupoli S, Goteri G, *et al.* Pegylated liposomal doxorubicin in the treatment of primary cutaneous T-cell lymphomas. *Haematologica* 2007;**92**:686–9.
16. Quereux G, Marques S, Nguyen JM, *et al.* Prospective multicenter study of pegylated liposomal doxorubicin treatment in patients with advanced or refractory mycosis fungoides or Sézary syndrome. *Arch Dermatol* 2008;**144**:727–33.
17. Grange F, Beylot-Barry M, Courville P, *et al.* Primary cutaneous diffuse large B-cell lymphoma, leg type: clinicopathologic features and prognostic analysis in 60 cases. *Arch Dermatol* 2007;**143**:1144–50.
18. Senff NJ, Hoefnagel JJ, Jansen PM, *et al.* Reclassification of 300 primary cutaneous B-cell lymphomas according to the new WHO-EORTC classification for cutaneous lymphomas: comparison with previous classifications and identification of prognostic markers. *J Clin Oncol* 2007;**25**:1581–7.
19. Bekkenk MW, Vermeer MH, Geerts ML, Noordijk EM, Heule F, van Voorst Vader PC, van Vloten WA, Meijer CJ, Willemze R. Treatment of multifocal primary cutaneous B-cell lymphoma: a clinical follow-up study of 29 patients. *J Clin Oncol* 1999;**17**:2471–8.
20. Kim YH, Willemze R, Pimpinelli N, Whittaker S, Olsen EA, Ranki A, Dummer R, Hoppe RT; ISCL and the EORTC. TNM classification system for primary cutaneous lymphomas other than mycosis fungoides and Sézary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC). *Blood* 2007;**110**:479–84.
21. Lorusso D, Di Stefano A, Carone V, Fagotti A, Pisconti S, Scambia G. Pegylated liposomal doxorubicin-related palmar-plantar erythrodysesthesia ('hand-foot' syndrome). *Ann Oncol* 2007;**18**:1159–64.
22. Lotem M, Hubert A, Lyass O, Goldenhersh MA, Ingber A, Peretz T, Gabizon A. Skin toxic effects of polyethylene glycol-coated liposomal doxorubicin. *Arch Dermatol* 2000;**136**:1475–80.
23. Soloman R, Gabizon AA. Clinical pharmacology of liposomal anthracyclines: focus on pegylated liposomal Doxorubicin. *Clin Lymphoma Myeloma* 2008;**8**:21–32.
24. Cheson BD, Pfistner B, Juweid ME, *et al.* Revised response criteria for malignant lymphoma. *J Clin Oncol* 2007;**25**:579–86.
25. Common Terminology Criteria for Adverse Events (CTCAE) version 3. Available at <http://www.fda.gov/cder/cancer/toxicityframe.htm> (last accessed date 9 August 2006).
26. Goteri G, Ranaldi R, Simonetti O, Capretti R, Menzo S, Stramazzotti D, Morichetti D, Offidani AM, Rupoli S, Leoni P. Clinicopathological features of primary cutaneous B-cell lymphomas from an academic regional hospital in central Italy: no evidence of *Borrelia burgdorferi* association. *Leuk Lymphoma* 2007;**48**:2184–8.
27. Senff NJ, Noordijk EM, Kim YH, *et al.* European Organization for Research and Treatment of Cancer (EORTC) and International Society for Cutaneous Lymphoma (ISCL) consensus recommendations for the management of cutaneous B-cell lymphomas. *Blood* 2008;**112**:1600–9.
28. Smith BD, Glusac EJ, McNiff JM, Smith GL, Heald PW, Cooper DL, Wilson LD. Primary cutaneous B-cell lymphoma treated with radiotherapy: a comparison of the European Organization for Research and Treatment of Cancer and the WHO classification systems. *J Clin Oncol* 2004;**22**:634–9.
29. Dreno B. Standard and new treatments in cutaneous B-cell lymphomas. *J Cutan Pathol* 2006;**33**(Suppl. 1):47–51.
30. Cozzio A, Kempf W, Schmid-Meyer R, Gilliet M, Michaelis S, Schärer L, Burg G, Dummer R. Intra-lesional low-dose interferon alpha2a therapy for primary cutaneous marginal zone B-cell lymphoma. *Leuk Lymphoma* 2006;**47**:865–9.
31. Fink-Puches R, Wolf IH, Zalaudek I, Kerl H, Cerroni L. Treatment of primary cutaneous B-cell lymphoma with rituximab. *J Am Acad Dermatol* 2005;**52**:847–53.
32. Kerl K, Prins C, Saurat JH, French LE. Intralesional and intravenous treatment of cutaneous B-cell lymphomas with the monoclonal anti-CD20 antibody rituximab: report and follow-up of eight cases. *Br J Dermatol* 2006;**155**:1197–200.
33. Dang NH, Fayad L, McLaughlin P, *et al.* Phase II trial of the combination of denileukin diftitox and rituximab for relapsed/refractory B-cell non-Hodgkin lymphoma. *Br J Haematol* 2007;**138**:502–5.
34. Dummer R, Hassel JC, Fellenberg F, *et al.* Adenovirus-mediated intralesional interferon-gamma gene transfer induces tumor regressions in cutaneous lymphomas. *Blood* 2004;**104**:1631–8.
35. Maza S, Gellrich S, Assaf C, Beyer M, Spilker L, Orawa H, Munz DL, Sterry W, Steinhoff M. Yttrium-90 ibritumomab tiuxetan radioimmunotherapy in primary cutaneous B-cell lymphomas: first results of a prospective, monocentre study. *Leuk Lymphoma* 2008;**49**:1702–9.
36. Cerroni L, Zöchling N, Pütz B, Kerl H. Infection by *Borrelia burgdorferi* and cutaneous B-cell lymphoma. *J Cutan Pathol* 1997;**24**:457–61.
37. Hoefnagel JJ, Vermeer MH, Jansen PM, *et al.* Primary cutaneous marginal zone B-cell lymphoma: clinical and therapeutic features in 50 cases. *Arch Dermatol* 2005;**141**:1139–45.
38. Senff NJ, Hoefnagel JJ, Neelis KJ, Vermeer MH, Noordijk EM, Willemze R; Dutch Cutaneous Lymphoma Group. Results of radiotherapy in 153 primary cutaneous B-cell lymphomas classified according to the WHO-EORTC classification. *Arch Dermatol* 2007;**143**:1520–6.
39. Stanway A, Rademaker M, Kennedy I, Newman P. Cutaneous B-cell lymphoma of nails, pinna and nose treated with chlorambucil. *Australas J Dermatol* 2004;**45**:110–3.
40. Kempf W, Dummer R, Schmid MH, Fritz T, Wüthrich B, Burg G. Intralesional cisplatin for the treatment of cutaneous B-cell lymphoma. *Arch Dermatol* 1998;**134**:1343–5.

41. Zackheim HS, Epstein EH Jr, Crain WR. Topical carmustine (BCNU) for cutaneous T cell lymphoma: a 15-year experience in 143 patients. *J Am Acad Dermatol* 1990;**22**:802–10.
42. Kodama K, Massone C, Chott A, Metze D, Kerl H, Cerroni L. Primary cutaneous large B-cell lymphomas: clinicopathologic features, classification, and prognostic factors in a large series of patients. *Blood* 2005;**106**:2491–7.
43. Sarris AH, Braunschweig I, Medeiros LJ, *et al.* Primary cutaneous non-Hodgkin's lymphoma of Ann Arbor stage I: preferential cutaneous relapses but high cure rate with doxorubicin-based therapy. *J Clin Oncol* 2001;**19**:398–405.
44. Fierro MT, Quaglino P, Savoia P, Verrone A, Bernengo MG. Systemic polychemotherapy in the treatment of primary cutaneous lymphomas: a clinical follow-up study of 81 patients treated with COP or CHOP. *Leuk Lymphoma* 1998;**31**:583–8.
45. Nagatani T, Miyazawa M, Matsuzaki T, Hayakawa H, Iemoto G, Kim ST, Baba N, Sugiyama A, Aihara M, Miyamoto H. A case of cutaneous B-cell lymphoma treated successfully with MACOP-B. *J Dermatol* 1993;**20**:40–4.
46. Fierro MT, Savoia P, Quaglino P, Novelli M, Barberis M, Bernengo MG. Systemic therapy with cyclophosphamide and anti-CD20 antibody (rituximab) in relapsed primary cutaneous B-cell lymphoma: a report of 7 cases. *J Am Acad Dermatol* 2003;**49**:281–7.
47. Goto H, Nishio M, Endo T, Sato N, Koizumi K, Fujimoto K, Sakai T, Kumano K, Obara M, Koike T. Effective in vivo purging with rituximab and autologous peripheral blood stem cell transplantation in a woman with CD5 positive primary cutaneous diffuse large B-cell lymphoma. *Eur J Haematol* 2005;**74**:526–8.
48. Bekkenk MW, Postma TJ, Meijer CJ, Willemze R. Frequency of central nervous system involvement in primary cutaneous B-cell lymphoma. *Cancer* 2000;**89**:913–9.
49. Van Doorn R, Van Haselen CW, van Voorst Vader PC, Geerts ML, Heule F, de Rie M, Steijlen PM, Dekker SK, van Vloten WA, Willemze R. Mycosis Fungoides: disease evolution and prognosis of 309 Dutch patients. *Arch Dermatol* 2000;**136**:504–10.